Published in final edited form as:

Neurobiol Aging. 2014 January ; 35(1): 64–71. doi:10.1016/j.neurobiolaging.2013.06.011.

Blood pressure decrease correlates with tau pathology and memory decline in hypertensive elderly

Lidia Glodzik, MD, PhD^{1,*}, Henry Rusinek, PhD², Elizabeth Pirraglia, MA¹, Pauline McHugh, MD¹, Wai Tsui, MS¹, Schantel Williams, RN¹, Megan Cummings¹, Yi Li, MD¹, Kenneth Rich, MD¹, Catherine Randall, MA¹, Lisa Mosconi, PhD¹, Ricardo Osorio, MD¹, John Murray¹, Henrik Zetterberg, MD, PhD^{3,4}, Kaj Blennow, MD³, and Mony de Leon, EdD¹

¹ Center for Brain Health, Department of Psychiatry, New York University School of Medicine, New York, USA

² Department of Radiology, New York University School of Medicine, New York, USA

³ Institute of Neuroscience and Physiology, Department of Psychiatry and Neurochemistry, the Sahlgrenska Academy at the University of Gothenburg, S-431 80 Mölndal, Sweden

⁴ UCL Institute of Neurology, Queen Square, London WC1N 3BG, UK

Abstract

In hypertension, cerebral blood flow regulation limits are changed, and the threshold for blood pressure at which perfusion is safely maintained is higher. This shift may increase the brain's vulnerability to lower blood pressure in subjects with vascular disease. We investigated whether longitudinal reduction in mean arterial pressure (MAP) was related to changes in CSF biomarkers of Alzheimer's disease in a group of cognitively healthy elderly with and without hypertension (HTN). The relationships between MAP, memory decline and hippocampal atrophy were also examined. Seventy-seven subjects (age 63.4±9.4, range 44–86 years; education 16.9±2.1, range 10–22 years; 60% women) were assessed twice, 2±0.5 years apart. At both time points, all subjects underwent full medical and neuropsychological evaluations, lumbar punctures and MRI examinations. Twenty-five subjects had HTN. Hypertensive and normotensive subjects did not differ in their CSF biomarkers, hippocampal volumes or memory scores at baseline. In the entire study group, the increase in p-tau₁₈₁ was associated with a decline in verbal episodic memory ($\beta = -.30$, $p = .01$) and hippocampal volume reduction ($\beta = -.27$, $p = .02$). However, longitudinal decrease in MAP was related to memory decline ($\beta = -.50$, $p = .01$) and an increase in p-tau₁₈₁ ($\beta = -.50$, $p = .01$) only in subjects with hypertension. Our findings suggest that the hypertensive group may be sensitive to blood pressure reductions.

Hypertension (HTN) affects more than a half of the US population over the age of 60 (Hajjar et al.2006). It causes vascular remodeling, lumen narrowing and rarefaction of small vessels (Levy et al.2001), contributes to the formation of atheromatous plaques in larger arteries (Kennelly et al.2009), and ultimately leads to the impairment of vascular function.

© 2013 Elsevier Inc. All rights reserved.

*Corresponding author: Lidia Glodzik, Center for Brain Health, Department of Psychiatry, NYU School of Medicine, 145 East 32nd Street, New York NY, 10016. Tel: (212) 263-5698, Fax: (212) 263-3270; Lidia.Glodzik@nyumc.org.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Other authors have nothing to disclose.

In normal conditions, autoregulatory mechanisms maintain a constant cerebral blood flow (CBF) over a wide range of mean arterial pressures (MAP) (Zazulia 2009). However, even in the healthy brain, cerebral regulation is better adapted to compensate for sudden increases rather than for decreases in blood pressure (Tzeng et al.2010). In longstanding HTN, CBF regulation limits are changed and thresholds for MAP at which CBF is maintained are shifted to higher levels (Zazulia 2009). This shift may increase the brain's vulnerability to hypoperfusion at lower blood pressure (BP) values (van Beek et al.2008), suggesting that higher pressure is needed to maintain an adequate flow.

Although midlife HTN is a well-documented risk factor for cognitive decline and Alzheimer disease (AD) later in life, there is substantial evidence that low BP late in life is also related to AD and cognitive impairment (Qiu et al.2005). The initial observation of an association between low BP and dementia in the group of oldest old (Verghese et al.2003;Guo et al. 1996) was subsequently extended to a broader population: in a combined Swedish and Dutch sample low baseline systolic and diastolic BP conferred a higher risk of dementia two years later, across all age strata. Interestingly, this association was observed only in the groups treated with antihypertensive drugs. Moreover, subjects with dementia at follow-up had greater (although non-significant) longitudinal BP decline than non-demented peers (Ruitenberg et al.2001). In line with this observation, den Heijer et al. found that a steeper reduction in diastolic BP over a period of 20 years was related to greater cortical atrophy (den Heijer et al.2003), and that only in subjects using antihypertensive medication low diastolic BP was related to smaller hippocampal and amygdalar volumes (den Heijer et al. 2005). The use of antihypertensive medication may indicate more advanced HTN and CBF autoregulation impairment, and suggest that this category of patients is susceptible to low BP.

Impairment of autoregulation may lead to hypoperfusion and hypoxia. In laboratory animals hypoxia activates gamma-secretase amyloidogenic pathway (Lee et al.2006), increases *BACE1* gene transcription and expression (Sun et al.2006), deposition of amyloid beta and formation of neuritic plaques (Sun et al.2006). In humans vascular disease is associated with increased neurofibrillary changes (Sparks et al.1995), and recently a massive surge in blood A levels was seen in survivors after cardiac arrest (Zetterberg et al.2011).

Little is known whether changes in blood pressure relate to markers of amyloid and neurofibrillary tangles, typical of AD in humans. We investigated the relationships between longitudinal changes in blood pressure and cerebrospinal fluid markers (CSF) biomarkers of AD in cognitively healthy elderly with and without HTN. Our hypothesis was that blood pressure decreases would be associated with unfavorable dynamics of AD biomarkers in subjects with HTN, who are possibly more sensitive to MAP reduction than controls. Since hippocampal volume loss (Glodzik-Sobanska et al.2005) and resulting memory impairment (Ball et al.1985) are major features of AD, we also examined the relationship between blood pressure reduction, memory decline and hippocampal atrophy.

METHODS

Participants

The study included 77 cognitively healthy individuals (age 63.4 ± 9.4 , range 44-86 years; education 16.9 ± 2.1 , range 10-22 years; 60% women) enrolled at the Center for Brain Health and Alzheimer Disease Center at NYU School of Medicine. All subjects were cognitively healthy elderly recruited as volunteers for longitudinal studies of brain aging and memory; all signed an IRB approved informed consent.

All participants received medical, neurological, psychiatric and neuropsychological evaluations, and underwent blood tests, lumbar punctures and MRI examinations (high resolution T1, T2 and FLAIR). Patients with confounding brain pathology (e.g. tumor, neocortical infarction) were excluded. Blood tests comprised: complete blood count, comprehensive metabolic panel, lipid profile, thyroid hormone tests and urinalysis. The clinical evaluation included an interview according to the Brief Cognitive Rating Scale (BCRS), rating on Global Deterioration Scale (Reisberg et al.1993) and Clinical Dementia Rating (Morris 1993). Based on clinical assessment, all subjects were diagnosed as cognitively healthy: with or without subjective memory complaints, but not fulfilling the criteria for mild cognitive impairment or dementia. All received a global CDR of 0. Subjects scoring ≥ 16 on the 17-item Hamilton Depression Scale were excluded (Bech et al.1986). The mean follow-up time was $1.98 \pm .50$ years, median 1.95, minimum 1.2, maximum 3.4, range 2.2. At follow-up three subjects received a rating of GDS=3, and a CDR of 0.5, corresponding to a diagnosis of mild cognitive impairment (Reisberg et al.1993;Morris 1993). At each occasion the presence of hypertension was determined based on current antihypertensive treatment or systolic blood pressure ≥ 140 mmHg, or diastolic blood pressure ≥ 90 mmHg (Chobanian et al.2003).

Blood pressure (BP) measurements were taken in a sitting position after five min. rest. If patient was not treated but high blood pressure was identified, the diagnosis of HTN was assigned only if high BP was further confirmed during other visits to our Center. The MAP was calculated as:

$$1/3 \text{ systolic BP} + 2/3 \text{ of diastolic BP}$$

Longitudinal MAP rate of change (Rc) was calculated as:

$$R_c \text{ MAP} = (\text{MAP}_{\text{follow-up}} - \text{MAP}_{\text{baseline}}) / \text{time between examinations}$$

Hypercholesterolemia was established based on current treatment with lipid lowering medication and/or cholesterol levels ≥ 200 mg/dL (NIH Publication No.02-5125 and US Department of Health and Human Services 2002). Diabetes was defined as current treatment with glucose lowering medication and/or fasting glucose levels ≥ 126 mg/dL (American Diabetes Association 2010). Smoking was determined based on clinical interview. For each individual we calculated Framingham Cardiovascular Risk Profile (NIH Publication No.02-5125 and US Department of Health and Human Services 2002). Finally Body Mass Index (BMI) was calculated as:

$$\text{weight (lb)} \times 703 / \text{height (in)}^2$$

Apolipoprotein E (ApoE) genotyping was performed using polymerase chain reaction as previously described (Main et al.1991). Study subjects were classified as ApoE4 positive (ApoE4+) if they had one or two E4 alleles and otherwise negative (ApoE4-). Data was available for 76 subjects.

Memory testing

The measures included subtests of the Guild Memory Scale (Gilbert 1970). The Guild Memory scale was established in 1968 (Gilbert 1970). It includes subscales assessing immediate and delayed recall of orally presented paragraphs and verbal paired associates, digit span and recall of geometric design (Crook et al.1980). In this study we used four

subtests pertaining to episodic verbal memory: immediate and delayed recall of orally presented paragraphs and verbal paired associates. Higher scores indicate better performance. The Guild Memory test has been used at our Center for over 30 years and has a good track record of predicting decline in NYU population (Kluger et al.1999).

At both time points, test results were converted to age, education and gender adjusted standardized scores (z-scores) based on a normative population from our cohort (De Santi et al.2008). We subsequently calculated a composite score, which constituted an average of four tests. To analyze longitudinal change, the rate of change was calculated as:

$$R_c \text{Memory} = (Z\text{-score}_{\text{follow-up}} - Z\text{-score}_{\text{baseline}}) / \text{time between examinations}$$

General cognitive abilities were tested with Mini Mental State Examination (MMSE) (Folstein et al.1975).

Lumbar puncture, CSF collection and assays

Using a 25G needle guided by fluoroscopy, 15 ml of CSF was collected into three polypropylene tubes. All CSF samples were kept on ice until centrifuged for 10 min at 1500 *g* at 4 C. Samples were aliquoted to 0.25 ml polypropylene tubes and stored in at -80°C until the assay. All samples were blindly analyzed in batch mode. The concentrations of total tau (t-tau) (Blennow et al.1995) tau phosphorylated at threonine 181(p-tau₁₈₁) (Vanmechelen et al.2000) and amyloid 42 (A 42) (Andreasen et al.1999) were determined. Intra- and inter-assay coefficients of variation were <10% for all analytes. The rates of change were calculated as:

$$R_c \text{biomarker} = (\text{biomarker}_{\text{follow-up}} - \text{biomarker}_{\text{baseline}}) / \text{time between examinations}$$

Brain imaging

T1 weighted MRI scans were uniformly acquired in the coronal orientation (slice thickness: 1.6 mm field of view (FOV) 25 cm, number of excitations (NEX)= 1, matrix = 256×192, repetition time (TR)= 35 ms, time to echo (TE)= 9 ms, flip angle (FA)= 60°), using a 1.5 T GE scanner (GE, Milwaukee, WI, USA). Intracranial volumes, V_{IC} , were obtained using MRIcro (Rorden and Brett 2000). Hippocampal volumes (HipV) were obtained using FreeSurfer version 4.5.0: a set of tools for brain volumes reconstruction (Fischl et al.2002). Hippocampal volume was presented as a percentage of V_{IC} : fHipV defined as HipV / V_{IC} . Left and right HipV were averaged. Hippocampal volume rates of change were expressed as:

$$R_c \text{fHipV} = (\text{fHipV}_{\text{follow-up}} - \text{fHipV}_{\text{baseline}}) / \text{time between examinations}$$

Hippocampal data was not available for 4/77 subjects, due to poor image quality.

Statistical analysis

Continuous demographic measures were examined using t-test. Categorical variables were examined with χ^2 test.

General linear models were used to compare CSF biomarkers, hippocampal volumes, memory performance and their respective longitudinal rates of change between HTN groups. MANCOVA was used to examine inter-correlated variables (CSF biomarkers),

ANCOVA for memory scores and fHipV. If dependent variables deviated from normality analyses were repeated with rank-transformed values. All models initially included age, gender, education and ApoE4 status. These covariates were retained only if they significantly contributed to the model.

Baseline and follow-up values in the entire group were compared using paired t-tests.

We confirmed longitudinal changes using random coefficient analysis (RCA). In all analyses age, gender, education, ApoE status and time to follow-up were included. We also used RCA to confirm whether variables of interest were changing differently in the HTN+ and HTN- groups. RCA models included hypertension status, age, gender, education, ApoE status, time to follow-up and interaction between hypertension status and time. For each analyzed variable a model with the best fit (based on Akaike Information Criteria: AIC) was chosen.

Linear regression (LR) was used to analyze associations between variables of interest. The interaction term was used to determine whether associations differed in the HTN+ and HTN- groups. It was done as follows:

- i. HTN status, MAP (or R_cMAP), and the interaction between HTN and MAP (i.e., $HTN \times MAP$ or $HTN \times R_cMAP$) were examined as predictors of CSF biomarkers, memory performance, and hippocampal volumes (or their rates of change).
- ii. HTN status, CSF biomarkers (or change in CSF biomarkers), and the interaction between HTN and CSF biomarkers ($HTN \times biomarker$ or $HTN \times R_cbiomarker$) were examined as predictors of memory performance and hippocampal volumes (or their rates of change).
- iii. HTN status, hippocampal volume (or the R_cfHipV), and the interaction between HTN and hippocampal volume ($HTN \times fHipV$ or $HTN \times R_cfHipV$) were examined as predictors of memory performance (or its rate of change).

If significant interaction was detected, the relationships between dependent variable and predictor were further examined within HTN+ and HTN- groups with linear regression.

All the LR models initially included age, gender, and education. They were retained only if they significantly contributed to the model. If dependent variables deviated from normality analyses were repeated after removing outliers and on log transformed data to confirm the results. Standardized β coefficients are reported.

Statistical analyses were performed with SPSS 16, Chicago IL, with p values declared statistically significant when <0.05 .

RESULTS

Hypertension

Baseline—At baseline HTN was present in 25 (33%) subjects. One additional subject was diagnosed with HTN at follow-up. HTN+ group refers to subjects with HTN at baseline. The diagnosis of hypertension was based on current treatment with antihypertensive medication for 18 subjects. For seven subjects, high blood pressure measurement at baseline was the basis for classification to the HTN+ group. Three of them were treated with BP lowering medication at follow-up; for the remaining four, reviews of medical records from other evaluations at our Center revealed repeated high BP levels.

The HTN+ group was older ($p=.001$), had significantly higher MAP ($p<.001$), systolic ($p<.001$) and diastolic ($p=.005$) blood pressure (Table 1). The HTN+ group had a higher Framingham Cardiovascular Risk Profile than the HTN- group ($p=.02$). The groups did not differ in the prevalence of hypercholesterolemia, diabetes or smoking. Hypertensive subjects had higher BMI ($p=.045$) (Table 1). The prevalence of ApoE4 positivity did not differ between HTN groups (Table 1).

No differences were found in baseline CSF biomarkers levels. Neither baseline fHipV nor baseline memory score differ between groups (Table 1).

Detailed information about antihypertensive medication is presented in Table 2. The percentage of subjects taking statins was similar among normo- and hypertensive subjects (25 vs. 28%).

Longitudinal changes—The time between evaluations did not differ between HTN groups.

In the entire group $p\text{-tau}_{181}$ increased significantly over time ($p=.004$); $t\text{-tau}$ showed a similar trend ($p=.09$); A₄₂ did not change. Rates of change in biomarkers did not differ between HTN+ and HTN- groups. Hippocampal volume decreased ($p<.001$). $R_c\text{fHipV}$ was smaller in the HTN+ group ($p=.06$), indicating a greater atrophy rate; however hippocampal volumes were not different at follow-up.

In the entire group the composite memory score increased over time (trend: $p=.06$). Similarly to baseline, memory performance did not differ at follow-up between HTN+ and HTN- groups; rates of change were also similar (Table 1).

MAP did not change significantly. $R_c\text{MAP}$ did not correlate with age; and was similar in both HTN groups (Table 1). In addition, $R_c\text{MAP}$ nor did it differ between hypertensive subjects who at baseline were or were not on medication.

RCA confirmed the results of longitudinal comparisons.

Blood pressure and CSF biomarkers

No relationship was found between CSF biomarkers and MAP at baseline. Longitudinally, in the model where $R_{cp}\text{-tau}_{181}$ was predicted with $R_c\text{MAP}$, HTN group, and $HTN \times R_c\text{MAP}$ interaction, the interaction was significant (model $p=.01$, interaction $p=.02$), indicating that the relationship between $R_c\text{MAP}$ and $R_{cp}\text{-tau}_{181}$ was dependent on the presence or absence of HTN. Only in the hypertensive group was the decrease in MAP related to the increase in $p\text{-tau}_{181}$ ($\beta = -0.50$, $p=.01$) (Figure 1a).

No relationship was found between $R_{ct}\text{-tau}$ or $R_{cA_{42}}$ and $R_c\text{MAP}$.

Blood pressure and memory performance

No relationship was found between MAP and memory performance at baseline. Longitudinally, in a model predicting rate of change in episodic verbal memory, we found a significant $HTN \times R_c\text{MAP}$ interaction (model $p=.002$, interaction $p<.001$): Only among hypertensive subjects was the MAP increase related to the improvement in memory ($\beta = 0.50$, $p=.01$) (Figure 1b).

Blood pressure and hippocampal atrophy

We did not find any relationship between BP and hippocampal volume at baseline or longitudinally.

CSF biomarkers and memory performance

No relationship was found between CSF biomarkers and memory performance at baseline. Longitudinally, in the entire group p-tau₁₈₁ increase was associated with reduction in verbal episodic memory (model $p=.01$; $R_{cp}\text{-tau}_{181} \beta=-.30$, $p=.01$) (Figure 1c).

CSF biomarkers and hippocampal atrophy

We did not find any relationship between CSF biomarkers and hippocampal volume at baseline. Longitudinally, in the entire group there was a significant inverse relationship between $R_{c}\text{fHipV}$ and $R_{cp}\text{-tau}_{181}$ (model $p=.02$; $R_{cp}\text{-tau}_{181} \beta=-.27$, $p=.02$) (Figure 1d). Greater volume reductions in the hippocampus were associated with greater increases in p-tau₁₈₁.

Hippocampal atrophy and memory performance

We did not find any relationship between hippocampal volume and memory at baseline or longitudinally.

DISCUSSION

In subjects with hypertension, a longitudinal decline in blood pressure was associated with an increase in CSF phosphorylated tau and with worsening of verbal episodic memory. These relationships were not observed in the normotensive group. In the entire study group, the increase in p-tau₁₈₁ was associated with a decline in verbal episodic memory and hippocampal volume reduction.

Our findings extend previous observations that a decline in blood pressure was related to dementia (Ruitenberg et al.2001) and brain damage (den Heijer et al.2003), and that these associations were primarily found in individuals treated with antihypertensive drugs (den Heijer et al.2005;Ruitenberg et al.2001). A recent study of subjects with symptomatic arterial disease from the SMART cohort found that lower BP was also associated with worse self-assessment of physical and mental health (Muller et al.2013). The presence of hypertension or arterial disease may indicate impairment of cerebral autoregulation and thus increased vulnerability to BP changes and in particular to low BP. Earlier reports from the SMART group showed that the greatest reduction in CBF at 4 year follow up was observed in subjects who had high baseline BP and low or high BP at follow-up (Muller et al.2012). In the same cohort, lower total CBF was related to greater subcortical atrophy only in the presence of a high load of white matter lesions (Appelman et al.2008). Others found that an increase in volume of white matter hyperintensities was related to longitudinal BP fluctuations, and lesions progressed fastest in subjects with high and variable BP (Brickman et al.2010). At constant intracranial pressure, cerebral perfusion pressure is dependent on MAP (Steiner and Andrews 2006). Although a healthy brain maintains constant CBF within a broad range of BP values (Zazulia 2009), recent evidence indicates that even in healthy subjects the CBF is not completely independent from BP: a MAP change of 1 mm of mercury resulted in 0.82% change in middle cerebral artery blood flow velocity (Lucas et al. 2010). In hypertension, hypertrophy and remodeling of the vessels ultimately lead to impairment of blood flow regulation and render hypertensive subjects more susceptible to adverse effects of BP changes (Zazulia 2009). Since CBF measurements were not available in our study, we can only conjecture that MAP decreases in the HTN group might have been associated with CBF reduction.

Animal studies showed that even mild and transient hypoperfusion resulted in exaggerated tau phosphorylation (despite overall reductions in tau levels) and long lasting increases of amyloid beta (Koike et al.2010). Cerebral ischemia potentiated neurotoxic effects of A

injections and increased the number of phosphorylated tau positive cells (Li et al.2011). In humans, the presence of the ApoE 4 allele and hypertension were related to higher tau and ptau₁₈₁ (Kester et al.2010). Despite a substantial body of evidence linking ischemic injury and amyloid accumulation (Koike et al.2010;Lee et al.2006), we did not see any association between MAP changes and A₄₂. Possibly, different processes may play a role in our group. For example, kinase activity (Fang et al.2010) or p-tau clearance may be more affected than A₄₂ pathways.

In hypertensive subjects, longitudinal MAP reduction was not only concomitant with a p-tau₁₈₁ increase but also with decline in verbal episodic memory. The hippocampus is crucial for storage and retrieval of episodic memories(Frank et al.2006). It is also particularly sensitive to hypoperfusion (Zola-Morgan et al.1992;Zarow et al.2005). In our study, hippocampal atrophy was also related to p-tau₁₈₁ increase. These observations allow us to envision the sequence in HTN+ subjects: reduction in MAP might lead to CBF decrease, accumulation of neurofibrillary pathology, hippocampal atrophy and memory decline. Nonetheless, in opposition to an earlier report by den Heijer et al. (2005), we did not find an association between BP decline and hippocampal volume. Conceivably, p-tau₁₈₁ changes preceded volume reductions. We also did not observe a relationship between memory and hippocampal atrophy. Possibly the automated hippocampal segmentation employed in this study was not sensitive enough and other methods, such as manual segmentation, would have been more appropriate.

Change in p-tau₁₈₁ correlated with a decline in cognition and hippocampal atrophy. We did not find a relationship between A₄₂ and cognitive performance or volumetric measurements. This, however, is not surprising, given our previous findings that p-tau but not A₄₂ correlated with memory performance in the cognitively intact elderly (Glodzik et al.2011). In addition, others also reported stronger correlations between tau and cognition than between A₄₂ and cognition (Lin et al.2009). Longitudinal changes in biomarkers reached significance for p-tau₁₈₁ and t-tau. This is in agreement with a previous observation that tau changes were more pronounced than A₄₂ dynamics over a short period of time (Jack, Jr. et al.2011). In the group as a whole, hippocampal volumes decreased, as expected. Memory scores increased, most likely reflecting learning effects.

Hypertensive and normotensive subjects did not differ in their CSF biomarker concentrations. Despite the growing recognition that vascular risk factors may have an impact on the development of AD, it is not clear whether increased cardiovascular risk translates into more abnormal CSF AD markers in humans. Interestingly, some neuropathological studies showed no increase in amyloid or neurofibrillary pathology with more advanced vascular brain damage (Schneider 2009), while other reports (Sparks et al. 1995) and animal data (Sun et al.2006;Koike et al.2010) suggest that vascular disease can intensify AD pathology. The HTN+ group had a higher Framingham Cardiovascular Risk Profile score. This is expected since the score itself is calculated based on the level of systolic blood pressure and use of antihypertensive medication. BMI was also higher in the HTN+ group. It is not clear whether BMI is related to CSF biomarkers. Previous work indicates that the prevalence of abnormal biomarkers was higher rather in subjects with normal weight compared to overweight individuals (Vidoni et al.2011). Altogether, we believe that our results were not biased by an imbalance in risk factors.

We specifically investigated MAP. This measure, incorporating both systolic and diastolic BP, may be more closely correlated with brain perfusion pressure (Steiner and Andrews 2006) than either systolic or diastolic BP alone. MAP may also be better than pulse pressure, which is primarily an indicator of vascular stiffness (Safar et al.2012). The reason for possible BP reductions remains unclear. The HTN+ group had higher MAP at baseline and

follow-up. Despite numerical differences (higher in HTN+), R_c MAP was not different between HTN groups, nor was it related to age. In addition, among subjects with HTN, we did not find evidence that pharmacologically treated subjects had greater MAP reductions than those who were not treated. However, our small sample size precludes us from drawing definite conclusions. The baseline MAP of the hypertensive group was within normal range. This may suggest that any further BP decrease may prove adverse. Our findings add to the discussion regarding the importance of determining an optimal BP for an individual. While recent studies show positive effects of anti-hypertensive therapy on the reduction of stroke and heart attack, the cognitive benefits from treatment are less compelling (Birns and Kalra 2009; McGuinness et al. 2009).

The study had several limitations. Subjects were highly educated, highly functioning, and predominantly Caucasian, with moderate overall levels of vascular risk. This lack of heterogeneity in our sample and its relatively small size make the generalizability of the findings difficult. Furthermore, since we did not adjust for the effects of antihypertensive medication or their types, the results can be biased by different properties of BP lowering agents. Statistical analysis included many comparisons. Within each studied relationship (CSF biomarkers- BP, CSF biomarkers- memory performance, and CSF biomarkers – hippocampal volume), we have tested three models (one for each biomarker), and the p threshold for a significant effect was $0.05/3 = 0.01666 \approx 0.02$. With a more conservative approach (number of relationships studied* number of CSF biomarkers, $p=0.05/9 \approx 0.006$), some results would not reach significance. Finally, we assumed that CSF tau and A β 42 in cognitively healthy elderly are related to the AD process. However, it is not clear whether they indicate future disease or are a common response to multiple insults that occur with aging. Since none of the study subjects declined to AD at follow-up, we were not able to address the question of whether unfavorable biomarker dynamics will ultimately lead to a disease.

Despite these limitations, our data suggest that while an increase in p-tau $_{181}$ is generally associated with a decline in verbal episodic memory and hippocampal volume reduction, in subjects with hypertension p-tau $_{181}$ increases and memory decline may be attributed to longitudinal decreases in BP. Prospective studies will help to determine whether such decreases result from impaired cerebral autoregulation and cause CBF reduction in subjects with established vascular disease. Our observations may have a potential impact on management of hypertension if confirmed by larger studies stratified for different types of antihypertensive medication.

Acknowledgments

This study was supported by the following grants: NIH-NIA AG12101, AG08051, AG022374 and HL-111724-01.

Financial Disclosures:

Dr. Glodzik was a PI on an Investigator Initiated project funded by Forest Laboratories, Inc, and received an honorarium for serving as a consultant to Roche Pharma.

Drs. Mosconi, Tsui and de Leon have a patent on a technology that was licensed to Abiant Imaging Inc. by NYU and, as such, have a financial interest in this license agreement and hold stock and stock options on the company. Drs. Mosconi and de Leon have received compensation for consulting services from Abiant Imaging.

Dr. Blennow has served at an Advisory Board for Innogenetics, Ghent, Belgium.

Dr. de Leon has received personal compensation for serving as a consultant for Abiant Imaging Inc. (Chicago, IL). He was also a PI on a completed Investigator Initiated project funded by Forest Laboratories, Inc., and a completed clinical trial supported by Neuroptix (Boston). Dr. de Leon received an honorarium for serving on the French Alzheimer Disease Foundation and as a consultant to Roche Pharma.

Reference List

- American Diabetes Association. Standards of medical care in diabetes--2010. *Diabetes Care*. 2010; 33(Suppl 1):S11–S61. [PubMed: 20042772]
- Andreasen N, Hesse C, Davidsson P, Minthon L, Wallin A, Winblad B, et al. Cerebrospinal fluid beta-amyloid(1-42) in Alzheimer disease: differences between early- and late-onset Alzheimer disease and stability during the course of disease. *Arch Neurol*. 1999; 56:673–680. [PubMed: 10369305]
- Appelman AP, van der Graaf Y, Vincken KL, Tiehuis AM, Mali WP, Geerlings MI, et al. Total cerebral blood flow, white matter lesions and brain atrophy: the SMART-MR study. *J Cereb Blood Flow Metab*. 2008; 28:633–639. [PubMed: 17912270]
- Ball MJ, Hachinski V, Fox A, Kirshen AJ, Fisman M, Blume W, et al. A new definition of Alzheimer's disease: A hippocampal dementia. *Lancet*. 1985; 1:14–16. [PubMed: 2856948]
- Bech P, Kastrup M, Rafaelsen OJ. Mini-compendium of rating scales for states of anxiety depression mania schizophrenia with corresponding DSM-III syndromes. *Acta Psychiatr Scand Suppl*. 1986; 326:1–37. [PubMed: 3458353]
- Birns J, Kalra L. Cognitive function and hypertension. *J Hum Hypertens*. 2009; 23:86–96. [PubMed: 18650838]
- Blennow K, Wallin A, Agren H, Spenger C, Siegfried J, Vanmechelen E. Tau protein in cerebrospinal fluid: a biochemical marker for axonal degeneration in Alzheimer disease? *Molecular & Chemical Neuropathology*. 1995; 26:231–245. [PubMed: 8748926]
- Brickman AM, Reitz C, Luchsinger JA, Manly JJ, Schupf N, Muraskin J, et al. Long-term blood pressure fluctuation and cerebrovascular disease in an elderly cohort. *Arch Neurol*. 2010; 67:564–569. [PubMed: 20457955]
- Chobanian A, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr. et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *JAMA*. 2003; 289:2560–2572. [PubMed: 12748199]
- Crook T, Gilbert JG, Ferris SH. Operationalizing memory impairment in elderly persons: The Guild Memory Test. *Psychological Reports*. 1980; 47:1315–1318. [PubMed: 7220760]
- De Santi S, Pirraglia E, Barr WB, Babb J, Williams S, Rogers K, et al. Robust and conventional neuropsychological norms: Diagnosis and prediction of age-related cognitive decline. *Neuropsychology*. 2008; 22:469–484. [PubMed: 18590359]
- den Heijer T, Launer LJ, Prins ND, van Dijk EJ, Vermeer SE, Hofman A, et al. Association between blood pressure, white matter lesions, and atrophy of the medial temporal lobe. *Neurol*. 2005; 64:263–267.
- den Heijer T, Skoog I, Oudkerk M, de Leeuw FE, de Groot JC, Hofman A, et al. Association between blood pressure levels over time and brain atrophy in the elderly. *Neurobiol Aging*. 2003; 24:307–313. [PubMed: 12498964]
- Fang H, Zhang LF, Meng FT, Zhou JN. Acute hypoxia promote the phosphorylation of tau via ERK pathway. *Neuroscience Letters*. 2010; 474:173–177. [PubMed: 20304032]
- Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, et al. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron*. 2002; 33:341–355. [PubMed: 11832223]
- Folstein MF, Folstein SE, McHugh PR. Mini-mental state: A practical method for grading the cognitive state of patients for the clinician. *J Psychiat Res*. 1975; 12:189–198. [PubMed: 1202204]
- Frank LM, Brown EN, Stanley GB. Hippocampal and cortical place cell plasticity: implications for episodic memory. *Hippocampus*. 2006; 16:775–784. [PubMed: 16921502]
- Gilbert, JG. Guild Memory Test Manual. UNICO National Mental Health Research Center; Newark,NJ: 1970.
- Glodzik L, De Santi S, Tsui WH, Mosconi L, Zinkowski R, Pirraglia E, et al. Phosphorylated tau 231, memory decline and medial temporal atrophy in normal elders. *Neurobiology of Aging*. 2011; 32:2131–2141. [PubMed: 20133017]
- Glodzik-Sobanska L, Rusinek H, Mosconi L, Li Y, Zhan J, De Santi S, et al. The role of quantitative structural imaging in the early diagnosis of Alzheimer's disease. *Neuroimaging Clinics of North America*. 2005; 15:803–826. [PubMed: 16443492]

- Guo Z, Viitanen M, Fratiglioni L, Winblad B. Low blood pressure and dementia in elderly people: the Kungsholmen project. *BMJ*. 1996; 312:805–808. [PubMed: 8608286]
- Hajjar I, Kotchen JM, Kotchen TA. Hypertension: Trends in Prevalence, Incidence, and Control. *Annu Rev Public Health*. 2006; 27:465–490. [PubMed: 16533126]
- Jack CR Jr, Vemuri P, Viste HJ, Weigand SD, Aisen PS, Trojanowski JQ, et al. Evidence for Ordering of Alzheimer Disease Biomarkers. *Arch Neurol*. 2011; 68:1526–1535. [PubMed: 21825215]
- Kennelly SA, Lawlor B, Kenny RA. Blood pressure and the risk for dementia—A double edged sword. *Aging Reaserch Reviews*. 2009; 8:61–70.
- Kester MI, van der Flier WM, Mandic G, Blankenstein MA, Scheltens P, Muller M. Joint effect of hypertension and APOE genotype on CSF biomarkers for Alzheimer's disease. *J Alzheimer's Dis*. 2010; 20:1083–1090. [PubMed: 20413898]
- Kluger A, Ferris SH, Golomb J, Mittelman MS, Reisberg B. Neuropsychological prediction of decline to dementia in nondemented elderly. *J Geriatr Psychiat Neurol*. 1999; 12:168–179.
- Koike MA, Green KN, Blurton-Jones M, LaFerla FM. Oligemic hypoperfusion differentially affects tau and amyloid-beta. *Am J Pathol*. 2010; 177:300–310. [PubMed: 20472896]
- Lee PH, Hwang EM, Hong HS, Boo JH, Mook-Jung I, Huh K. Effect of ischemic neuronal insults on amyloid precursor protein processing. *Neurochem Res*. 2006; 31:821–827. [PubMed: 16794858]
- Levy BI, Ambrosio G, Pries AR, Struijker-Boudier HA. Microcirculation in hypertension: a new target for treatment? *Circulation*. 2001; 104:735–740. [PubMed: 11489784]
- Li J, Wang Y-J, Zhang M, Fang C-Q, Zhou H-D. Cerebral ischemia aggravates cognitive impairment in a rat model of Alzheimer's disease. *Life Sci*. 2011; 89:86–92. [PubMed: 21620868]
- Lin YT, Cheng JT, Yao YC, Juo LI, Lo YK, Lin CH, et al. Increased total tau but not amyloid-*beta*₄₂ in cerebrospinal fluid correlates with short-term memory impairment in Alzheimer's disease. *Journal of Alzheimer's Disease*. 2009; 18:907–918.
- Lucas SJE, Tzeng YC, Galvin SD, Thomas KN, Ogoh S, Ainslie PN. Influence of Changes in Blood Pressure on Cerebral Perfusion and Oxygenation. *Hypertension*. 2010; 55:698–705. [PubMed: 20083726]
- Main BF, Jones PJ, MacGillivray RT, Banfield DK. Apolipoprotein E genotyping using the polymerase chain reaction and allele-specific oligonucleotide primers. *J Lipid Res*. 1991; 32:183–187. [PubMed: 2010690]
- McGuinness B, Todd S, Passmore P, Bullock R. Blood pressure lowering in patients without prior cerebrovascular disease for prevention of cognitive impairment and dementia. *The Cochrane Collaboration*. 2009
- Morris JC. The Clinical Dementia Rating (CDR): Current version and scoring rules. *Neurol*. 1993; 43:2412–2414.
- Muller M, Jochemsen HM, Visseren FLJ, Grool AM, Launer LJ, van der Graaf Y, et al. Low blood pressure and antihypertensive treatment are independently associated with physical and mental health status in patients with arterial disease: the SMART study. *J Intern Med*. 2013 n/a.
- Muller M, van der Graaf Y, Visseren FL, Mali WPT, Geerlings MI, for the SMART Study Group. Hypertension and longitudinal changes in cerebral blood flow: The SMART-MR study. *Ann Neurol*. 2012; 71:825–833. [PubMed: 22447734]
- NIH Publication No.02-5125; US Department of Health and HUMAN Services NIOHNLBI. Third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation and treatment of high cholesterol in adults (Adult Treatment panel III). Final Report. *Circulation*. 2002; 106:3143. [PubMed: 12485966]
- Qiu C, Winblad B, Fratiglioni L. The age-dependent relation of blood pressure to cognitive function and dementia. *Lancet Neurology*. 2005; 4:487–499. [PubMed: 16033691]
- Reisberg B, Sclan SG, Franssen EH, de Leon MJ, Kluger A, Torossian CL, et al. Clinical stages of normal aging and Alzheimer's disease: The GDS staging system. *Neurosci Res Communications*. 1993; 13(Suppl. 1):551–554.
- Rorden C, Brett M. Stereotaxic display of brain lesions. *Behavioural Neurology*. 2000; 12:191–200. [PubMed: 11568431]

- Ruitenberg A, Skoog I, Ott A, Aevvarsson O, Witteman JCM, Lernfelt B, et al. Blood Pressure and Risk of Dementia: Results from the Rotterdam Study and the Gothenburg H-70 Study. *Dementia and Geriatric Cognitive Disorders*. 2001; 12:33–39. [PubMed: 11125239]
- Safar ME, Nilsson PM, Blacher J, Mimran A. Pulse pressure, arterial stiffness, and end-organ damage. *Current Hypertension Reports*. 2012; 14:339–344. [PubMed: 22555981]
- Schneider JA. High blood pressure and microinfarcts: a link between vascular risk factors, dementia, and clinical Alzheimer's disease. *JAGS*. 2009; 57:2146–2147.
- Sparks DL, Scheff SW, Liu H, Landers TM, Coyne CM, Hunsaker JCI. Increased incidence of neurofibrillary tangles (NFT) in non-demented individuals with hypertension. *Journal of the Neurological Sciences*. 1995; 131:162–169. [PubMed: 7595642]
- Steiner LA, Andrews PJD. Monitoring the injured brain: ICP and CBF. *Br J Anaesth*. 2006; 97:26–38. [PubMed: 16698860]
- Sun X, He G, Qing H, Zhou W, Dobie F, Cai F, et al. Hypoxia facilitates Alzheimer's disease pathogenesis by up-regulating BACE1 gene expression. *PNAS*. 2006; 103:18727–18732. [PubMed: 17121991]
- Tzeng YC, Willie CK, Atkinson G, Lucas SJE, Wong A, Ainslie PN. Cerebrovascular Regulation During Transient Hypotension and Hypertension in Humans. *Hypertension*. 2010; 56:268–273. [PubMed: 20547971]
- van Beek AH, Claassen JA, Rikkert MG, Jansen RW. Cerebral autoregulation: an overview of current concepts and methodology with special focus on the elderly. *J Cereb Blood Flow Metab*. 2008; 28:1071–1085. [PubMed: 18349877]
- Vanmechelen E, Vanderstichele H, Davidsson P, Van Kerschaver E, Van Der Perre B, Sjogren M, et al. Quantification of tau phosphorylated at threonine 181 in human cerebrospinal fluid: a sandwich ELISA with a synthetic phosphopeptide for standardization. *Neuroscience Letters*. 2000; 285:49–52. [PubMed: 10788705]
- Verghese J, Lipton RB, Hall CB, Kuslansky G, Katz MJ. Low blood pressure and the risk of dementia in very old individuals. *Neurol*. 2003; 61:1667–1672.
- Vidoni ED, Townley RA, Honea RA, Burns JM, for the Alzheimer's Disease Neuroimaging Initiative. Alzheimer disease biomarkers are associated with body mass index. *Neurol*. 2011; 77:1913–1920.
- Zarow C, Vinters HV, Ellis WG, Weiner MW, Mungas D, White L, et al. Correlates of Hippocampal Neuron Number in Alzheimer's Disease and Ischemic Vascular Dementia. *Ann Neurol*. 2005; 57:896–903. [PubMed: 15929035]
- Zazulia AR. Regulation of Cerebral Blood Flow in Untreated Mild-to-Moderate Hypertension. *Am J Hypertens*. 2009; 22:344. [PubMed: 19308024]
- Zetterberg H, Mortberg E, Song L, Chang L, Provuncher GK, Patel PP, et al. Hypoxia due to cardiac arrest induces a time-dependent increase in serum amyloid beta levels in humans. *PLoS One*. 2011; 6:e28263, 1–6. [PubMed: 22194817]
- Zola-Morgan S, Squire LR, Rempel NL, Clower RP, Amaral DG. Enduring memory impairment in monkeys after ischemic damage to the hippocampus. *The Journal of Neuroscience*. 1992; 12:2582–2596. [PubMed: 1613549]

Figure 1.

Relationships between rates of change in MAP ($R_c \text{MAP}$) and p-tau₁₈₁ ($R_c p\text{-tau}_{181}$) (a), rates of change in MAP and episodic verbal memory ($R_c \text{episodic memory}$) (b), rates of change in episodic verbal memory and p-tau₁₈₁ (c), rates of change in p-tau₁₈₁ and hippocampal volume ($R_c \text{Hippocampal volume}$) (d). Solid circles and solid lines – subjects with HTN. Diamonds and dashed lines - subjects without HTN. Units in the scales represent units per year: for p-tau pg/mL/year, for MAP mmHg/year, for episodic memory z-score unit/year, for hippocampal atrophy % of intracranial volume/year.

Table 1

Characteristics of the study group.

	Hypertension (n=25)			No Hypertension (n=52)		
	Baseline	Follow-up	Rate of change	Baseline	Follow-up	Rate of change
Age (year)	68.5±8.0 [*]			61.0± 9.2		
Gender (% female)	52%			63%		
Education (years)	17.2±2.0			16.7±2.2		
ApoE4 carriers	17%			37%		
Time between evaluations (years)	2.0± .50			1.9± .45		
Mean arterial pressure (mmHg)	97.0±12.0 [*]	92.6±11.5 [*]	−2.1±8.3	87.3± 9.8	86.6± 9.1	−.47±7.2
A 42 (pg/mL) ^a	596.6± 41.1	627.2±41.9	11.8±14.4	549.4±27.8	554.0±28.3	8.1±10.0
t-tau (pg/mL) ^a	264.6±27.2	285.0±26.2	9.9± 7.7	290.0±18.4	301.4±17.7	4.9±5.3
p-tau ₁₈₁ (pg/mL) ^a	48.5± 3.2	50.2±3.4	1.2± .80	47.6± 2.2	50.4±2.3	1.1± .60
Average fHipV (% of ICV) ^b	.30±.006	.29±.005	−.002±.001	.29±.004	.28±.004	−.000±.000
MMSE	29.7±.56	29.2±1.5		29.1±1.3	29.2±1.1	
Episodic verbal memory	.21±.71	.37±.92	.10±.38	−.10±.79	.04±.90	.09±.37
Framingham Cardiovascular Risk Profile ^c	8.6± .80 [*]			6.1±.55		
Hypercholesterolemia (%)	56%			60%		
Diabetes (%)	4%			0%		
Smoking (%)	0%			11%		
BMI	28.8±6.6 [*]			25.3±3.6		

For the remaining variables, the values are presented as mean ± standard deviation.

Rates of change are presented as unit per year

Memory measures are presented as z-scores

Framingham Cardiovascular Risk Profile represents % risk of coronary heart disease in the next 10 years

The results for hippocampal volume are presented for 73 subjects (25 HTN+ and 48 HTN-) BMI-Body Mass Index

^aThe results are given as mean ± standard error after accounting for age. No covariates were necessary for the rates of change.

^bThe results are given as mean ± standard error after accounting for age and gender. No covariates were necessary for atrophy rates.

^cThe results are given as mean ± standard error after accounting for age and gender.

* Significant at p<.05, comparisons between HTN+ and HTN- groups

Table 2

Antihypertensive medication status at baseline and follow-up.

Patient	ARB1	ACE-II	BB1	CCB1	Diuretic1	ARB2	ACE-I2	BB2	CCB2	Diuretic2
1	0	1	1	0	1	0	1	1	0	1
2	0	0	0	0	0	0	0	0	0	0
3	1	0	1	0	1	1	0	1	0	1
4	0	0	1	0	1	0	1	1	0	0
5	0	0	0	0	0	0	0	0	0	0
6	0	0	1	0	0	0	0	1	0	0
7	0	0	0	0	0	0	0	1	0	0
8	0	0	1	0	0	0	0	1	0	0
9	0	1	0	0	1	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0	0
11	0	1	0	0	0	0	1	0	0	0
12	0	0	0	0	0	0	0	0	0	0
13	0	0	0	0	0	1	0	0	0	0
14	0	0	0	1	1	0	0	0	1	1
15	0	0	1	0	0	0	0	1	0	0
16	0	0	0	0	1	0	0	0	0	1
17	0	0	1	0	1	0	0	1	0	1
18	0	0	0	0	0	0	0	0	0	0
19	1	0	0	0	0	1	0	1	0	0
20	0	1	0	0	0	0	1	0	0	1
21	0	1	1	0	0	0	1	1	0	0
22	0	0	0	0	0	0	0	1	0	0
23	1	0	1	0	1	1	0	1	0	0
24	0	1	1	0	1	0	1	1	0	0
25	0	0	1	0	0	0	0	1	0	0

ARB – angiotensin receptor blocker, ACE-I - angiotensin converting enzyme inhibitor, BB- betablocker, CCB – calcium channel blocker. Number 1 denotes time point 1: baseline, number 2 time point 2: follow-up.